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CONTROLLED RELEASE DRUG DELIVERY DEVICE

ABSTRACT

An oral drug delivery device for delivering a drug either intermittently or to a pre-selected region of the gastro-intestinal tract, particularly to the colon, consists of an a solid core comprising an active agent coated with a delay jacket, then coated with a semi-permeable membrane which is optionally drilled to provide a release orifice, and then optionally further coated with an enteric material. The device delivers substantially all of the active agent to the targeted site.

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CONTROLLED RELEASE DRUG DELIVERY DEVICE

The present invention relates to tablets which are time-controlled to release active agent intermittently or at a pre-selected region of the gastro-intestinal tract, specifically the colon.

Parametric drug delivery refers to drug release in synchrony with its temporal requirements or optimal absorption site, thereby maximizing therapeutic effect while simultaneously minimizing side-effects or *in vivo* degradation. An example of parametric drug delivery is delivery of a drug to a pre-selected region of the gastro-intestinal tract, such as the colon. Another example is delivery of a drug intermittently at pre-selected times such that the patient receives the drug when needed.

Delivery of a beneficial drug in the colon has been the goal of research projects. Many drugs are rendered ineffective by the enzymes present in the fluids of the upper gastro-intestinal tract, particularly protein or peptide-like drugs. Some drugs are more readily or more predictably absorbed by the colonic tissue than by that in the upper gastro-intestinal tract.

Delivery of a beneficial drug in the colon is also therapeutically indicated to treat diseased colonic tissue. In such circumstances, the drug should not be absorbed prior to localization in the colon lest its concentrations be diminished or even depleted prior to reaching the intended site of action. Such treatment would be beneficial for a variety of colonic diseases including inflammatory bowel disease, colitis ulcerosa, enteritis, regionalis Crohn, chronic nonspecific colitis, and diverticulitis.

Prior treatments have been attempted rectally using suppositories and enemas. Rectal administration, while often more effective than oral administration, is limited in that most rectally administrable dosage forms are capable of producing the intended result only in the immediate area, not reaching the upper portions of the colon. This is because the length of the colon reached is volume dependent, usually reaching only as far as the splenic flexure. Furthermore, if the patient suffers from severe inflammation of the

rectum, he may experience difficulty with retention enemas.

An orally administrable dosage form to treat colonic diseases would usually be preferred and is often required. Orally administrable treatments, using tablets, capsules, and the like, have been attempted. However, to reach the colon intact, the dosage form must withstand the rigors of the transit through the gastro-intestinal tract. These rigors include at least a million-fold variation in hydrogen ion concentration, wide variations in osmotic pressure from the surrounding fluids, a variety of enzymes, and a strong mechanical grinding force.

Most of these orally administered dosage forms result in delivery of the drug in the upper portion of the gastro-intestinal tract or, in the case of controlled release dosage forms, deliver drug throughout the entire length of the gastro-intestinal tract instead of concentrating delivery primarily within the colon. Thus, in either case, by the time the dosage form reaches the colon, the drug concentration is diminished or even depleted. In addition, the acidic and enzymatic environment of the stomach may inactivate a substantial amount of the drug, particularly protein or peptide-like drugs. Even if the drug is released from the stomach in its active state, such drugs frequently are metabolized or inactivated in the small intestine. Thus, little if any of the drug from these conventional dosage forms is available for producing a therapeutic result in the colon, especially if the dosage form reaches the colon essentially devoid of drug.

Drug delivery to the colon is also difficult because of the uncertainty of the transit time from oral ingestion to arrival at this pre-selected site. The time of retention within the stomach is most variable, depending both on the size of the dosage form and the amount of food present at the time of ingestion. The drug delivery device may remain within the stomach from about 0.5 to about ten hours. The device then enters the small intestine where retention time is significantly more constant and less dependent upon the amount of food present. It takes from about three to about six hours to travel the length of the small intestine to the beginning of the colon. The device may then remain within the colon from about ten to about fourteen hours in a subject with normal motility.

The time span necessary to delay release of the drug from an orally administered dosage form until the beginning of the colon is wide. This time span can be considerably narrowed by measuring the time from arrival in the small intestine instead of from the time of ingestion. Drug delivery in the stomach may be prevented by the use of an enteric coating which is resistant to the gastric fluids. As such a coating is not soluble in fluids

with an acidic pH, such as that of the stomach, application to the outside of the dosage form inhibits release prior to reaching the higher pH of the small intestine. Once the dosage form reaches the small intestine and the enteric coating dissolves, drug release needs to be delayed only an additional three to six hours to result in substantially no active agent being delivered before the colon.

Although some drug may reach the colon passively, conventional peroral dosage forms are not designed to deliver their contents specifically to the colon. Generally, they are formulated to be immediate release devices which disintegrate in the stomach, duodenum, or small intestine, allowing the drug to be immediately exposed to the local environment.

Controlled release dosage forms are known, for example Oral Osmotic Systems or OROS® (Alza Corporation). Although the benefits of controlled release are significant, such as reduction in the number of doses and steady drug levels in the blood, they are generally no more effective than conventional tablets in delivering the active agent primarily to the colon.

Several delivery forms have been developed which attempt to deliver active agent primarily to the colon. These methods rely upon either the environmental conditions surrounding the system, particularly pH, bacterial count and/or time.

Wong, et al. (US Patent Nos. 4,627,851; 4,693,895; and 4,705,515) disclose a tri-laminated core in which the first layer is composed of an insoluble, but semi-permeable composition, the second is a microporous combination of water insoluble polymer and osmotic solute, and the third contains an enteric composition. This dosage form has a delayed onset of delivery for a period of about two hours after it exits the stomach, after which only about 50% of the drug is released within twenty-four hours. This drug delivery time scheme is insufficient to insure that the bulk of the drug is delivered to the colon.

Theeuwes et al. (U.S. Patent No. 4,904,474) disclose a dosage form which has a two-layered internal compartment with a first layer of the drug in an excipient layer adjacent to an exit passageway and a second layer of a push component. The internal compartment is surrounded by a semi-permeable wall and then an enteric layer. This dosage form results in a delay of the onset of delivery in intestinal fluid for a period of about two hours. This represents a delay period too short, and a delivery rate too slow to insure the bulk of the drug is delivered to the colon.

Ring, et al. (WO 91/07949) disclose a tablet core coated with two laminates. The outer laminate is an erodible acrylic polymer and the inner laminate consists primarily of amylose in the glassy state which can only be degraded in the presence of fecal microflorae.

The instant parametric drug delivery devices can also be used to deliver a drug intermittently at pre-selected times such that the patient receives the drug when needed. This is of particular importance in treating diseases which have symptoms which do not remain constant throughout the day and night.

Blood pressure is known to follow a circadian rhythm during a 24-hour period. In some subjects the highest pressure occurs in the morning shortly after the individual awakes, suggesting that it would be appropriate to deliver an antihypertensive agent such as a ß-blocker to such a patient sufficiently before awakening so as to mitigate the effects of the disease at the most appropriate time interval. In order to accomplish this without disturbing the patient's sleep, it is necessary to administer the drug in the evening in a form that is activated just before the patient arises.

It is accordingly an object of the present invention to provide a delivery device for the oral administration of a pharmaceutically acceptable active agent to a warm-blooded animal, either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon.

It is another object of this invention to provide a dosage form for delivering substantially all of a therapeutic drug to the colon.

It is yet another object of this invention to provide a dosage form which comprises a core tablet coated with a delay jacket for delaying the delivery of the drug to insure the time required for the dosage form to travel through the small intestine.

It is still yet another object of this invention to provide a dosage form in which the semi-permeable membrane is still strong enough to resist the hydrostatic pressures of the osmotic core.

It is a further object of this invention to provide a dosage form which comprises an enteric coating over a semi-permeable wall for further delaying the delivery of the active agent during the time required for the dosage form to travel through the stomach.

It is still a further object of this invention to provide a dosage form which resists dissolution in gastric fluid for at least two hours, further delays initiation of active agent release for at least three hours, and releases at least 70% of its active agent within twenty-four hours.

It is yet still a further object of this invention to provide a delivery device which delivers drug intermittently at pre-selected times.

These, and other objects are accomplished by the present invention which pertains to an osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon. This drug delivery device comprises:
a) a solid core comprising an active agent;
b) a delay jacket coated over the core;
c) a semi-permeable membrane coated over the delay jacket, the membrane optionally having a release orifice; and optionally
d) an enteric coating over the semi-permeable membrane.

Such device resists dissolution in gastric fluid for at least two hours and thereafter limits the release of active agent in intestinal fluid to approximately ten percent or less for at least three hours after the device passes through the pylorus due to the delay jacket. The device thus allows for controlled continuous release of the active agent in the pre-selected region of the gastro-intestinal tract at a predetermined average rate, preferably at a rate of about 5 percent to about 25 percent by weight per hour. In addition, the device allows for substantially all of the active agent to be released at the pre-selected region of the gastro-intestinal tract, preferably 70-100% within twenty-four hours of ingestion.

Preferably, the device releases its active agent *in-vitro* according to the following scheme, where time is hours from inception corresponding to *in-vivo* release of active agent from time of ingestion:

Time (hrs.)	Fluid	Total Amount Released (%)
2	gastric	0 - 4
5	intestinal	0 - 10
6	intestinal	0 - 20
8	intestinal	0 - 50
10	intestinal	10 - 80
12	intestinal	20 - 100
18	intestinal	50 - 109
24	intestinal	70 - 115

Thus, the colonic delivery device would deliver from about 50% to about 100%, more particularly from about 60% to about 90%, most particularly from about 70% to about 80% of its active agent to the colon.

The solid core comprises an active agent and may optionally include other pharmaceutically acceptable excipients including osmotic agents, lubricants, glidants, wetting agents, binders, fillers, and suspending/thickening agents. Any core which would be suitable for an oral osmotic system may be used in the present invention, including the various modifications currently known in the art such as push-pull OROS.

Active agents useful in the core include, but are not limited to, proteins and peptides, antiasthmatics, antianginals, corticosteroids, 5-lipoxygenase inhibitors, antihypertensives, and leukotriene B_4 receptor antagonists. Proteins and peptides include, but are not limited to, transforming growth factors (TGF), immunoglobulin E (IgE) binding factors, interleukins, interferons (IFN), insulin-like growth factors (IGF), milk growth factors, anticoagulants, and parathyroid hormones (PTH). Specific active agents include theophylline, IGF-I, PTH (1-34) and analogues thereof, TGF_{α}, $TGF_{\beta 1}$, $TGF_{\beta 2}$, $TGF_{\beta 3}$, IFN_{α}, hybrid IFN_{α}, IFN_{γ}, N-hydroxy-N-((6-phenoxy-2H-1-benzopyran-3-yl)methyl)-urea, 4-[5-[4-(aminoiminomethyl)phenoxy]pentoxy]-3-methoxy-N,N-bis(1-methylethyl)-benzamide-(Z)-2-butenedioate, N-[2-[[2-[[4-(4-fluorophenyl)phenyl]methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxy]ethyl]-N-hydroxyurea, 1-(1-benzo[b]thien-2-ylethyl)-1-hydroxyurea, 5-[2-(2-carboxyethyl)-3-{6-(para-methoxyphenyl)-5E-hexenyl}oxyphenoxy]valeric acid, hirudin, heparin, calcitonin, 5-aminosalicylic acid, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, metoprolol fumarate, metoprolol tartrate, tetrahydroaminoacridine (THA), galanthamine, ursodiol,

clomipramine hydrochloride, terbutaline sulfate, aminoglutethimide, deferoxamine mesylate, estradiol, isoniazid, methyltestosterone, metyrapone, and rifampin. Of particular importance are theophylline, IGF-I, PTH (1-34) and analogues thereof, TGF_{α}, $TGF_{\beta 1}$, $TGF_{\beta 2}$, $TGF_{\beta 3}$, IFN_{α}, hybrid IFN_{α}, IFN_{γ}, hirudin, heparin, calcitonin, 5-aminosalicylic acid, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, and metoprolol. Virtually any other active agent which is known to be colonically absorbable or used to topically treat the colon can be used as an active agent in the present invention as long as it is compatible with the system components.

The core may include an osmotic agent if necessary or desirable to effect the desired release profile. The active agent, for example, metoprolol fumarate, may be sufficiently soluble to induce an internal hydrostatic pressure acceptable to eliminate the need for any additional osmotic agent. Suitable osmotic agents include pharmaceutically acceptable salts of inorganic and organic acids or nonionic organic acids of particularly high water solubility, e.g. carbohydrates such as sugar, or amino acids, or another active agent possessing suitable solubility.

Examples of water-soluble compounds for inducing osmosis in the core include inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof.

Additional core excipients include tabletting lubricants, glidants, wetting agents to aid in dissolution of the components, binders, and suspending/thickening agents. Suitable lubricants include calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate. Suitable glidants include fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents

include, but are not limited to, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9 or 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, 40, 60, or 80, sodium lauryl sulfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol (4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane). Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethyl cellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polyvinylmethacrylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable suspending/thickening agents include acacia, agar, alginic acid, bentonite, carbomer, carboxymethyl cellulose calcium, carageenan, carboxymethyl cellulose sodium, corn starch, dextrin, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, lecithin, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, pectin, poloxamer, polyethylene glycol alginate, polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, vinyl acetate, powdered cellulose, pregelatinized starch, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, and xanthan gum.

The delay jacket is included to impede the dissolution and release of the active agent for the time necessary for the drug delivery device to travel through the small intestine. The delay jacket is capable of attracting water across the semi-permeable membrane while also hindering the water from reaching the active core for the designated period of delay. The delay jacket will typically contain both water soluble, osmotically active components and insoluble and/or swellable components. The soluble osmotic agents leach out of the jacket and a suspension of at least some of the insoluble and/or swellable components remains. The active agent will later diffuse through this remaining suspension and thus the release of the active agent is dependent not only upon the composition of the inner core, but also upon the composition of the jacket.

The delay jacket comprises a binder, an osmotic agent, and a tablet lubricant. Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polyvinylmethacrylates,

polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable osmotic agents include, but are not limited to, inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof. Suitable tablet lubricants include calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Additional jacket excipients may include glidants and wetting agents. Suitable glidants include, but are not limited to, fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9 or 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20 or 40, polysorbate 60 or 80, sodium lauryl sulfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol® (4-(1,1,3,3-tetramethylbutyl)phenol) polymer with formaldehyde and oxirane).

Certain excipients may be included within the device to serve more than one function. For example, glucose may be included as a binder and/or an osmotic agent, and talc may be included as a glidant and/or a lubricant.

The delay jacket may be applied to the core using conventional means known in the technology, for example by using a tablet press or a spray coater. If applied as a solid, the delay jacket is preferably between about 125% and about 275%, and more preferably between about 150% and about 250% of the core by weight. If applied as a liquid, the delay jacket is between about 10% and about 100%, or between about 20% and about 80%, and preferably between about 30% and about 60% of the core by weight. However,

in both cases the ranges may vary based on the solution/suspension properties of the materials selected, and on the permeability properties of the rate controlling membrane.

The semi-permeable membrane is intended to be rigid enough so as to maintain the physical integrity of the tablet of the invention even in its environment of use without adversely affecting the active agent. The term "semi-permeable," as defined herein, refers to a membrane which, under identical conditions, transports different molecular species at different rates. In this case, the membrane is permeable to gastro-intestinal fluids, but is less permeable to the active agent or osmotic agent. If it is less permeable to the solubilized or suspended active agent or osmotic agent, it is necessary to include at least one release orifice through the membrane, while if it is permeable to the active agent or osmotic agent, the release orifice is optional.

The membrane comprises a material which can form films and typically comprises any of the porous membrane materials known in the tabletting art. Typical materials for forming the membranes are those known in the art to form osmosis or reverse osmosis membranes, including polycation-polyanion membranes. The porous membrane materials include cellulose acetate, ethylcellulose, polymethacrylic acid esters and acrylic acid ester/methacrylic acid copolymer with quarternary ammonium groups, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose ethers, cellulose acetate propionate, polyvinyl methyl ether polymers, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluene sulfonate, triacetate of locust bean gum, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated ethylenevinylacetate, polymeric epoxides, alkylene oxide-alkyl glycidyl ethers, polyurethanes, and polyglycolic acid. Preferably, the membrane material is cellulose acetate, ethylcellulose, polymethacrylic acid esters and acrylic acid ester/methacrylic acid copolymer with quarternary ammonium groups.

Alternatively, the semi-permeable membrane may be comprised of non-porous membrane materials in which pores have been formed. This is accomplished by including a water soluble pore-forming material in the insoluble, non-porous membrane material solution. When the membrane is exposed to an aqueous environment, the pore-forming material dissolves, resulting in the formation of pores. Thus, the porosity of the membrane is

directly proportional to the amount of pore-forming material incorporated into the membrane. The non-porous membrane materials include acrylics, polyurethanes, silicones, polyethylenes, polyvinyl chlorides, and ethylcellulose. The pore-forming materials include lactose, sucrose, mannitol, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and surfactants or other soluble additives.

The semi-permeable membrane may be applied using conventional film coating techniques known in the art, for example fluidized bed spraying. The choice of semi-permeable membrane plays an important role in controlling the release of the active agent. For example, it is known that the acetyl value is an important factor in determining the release rate from membranes constructed from cellulose acetate. Compendial grade cellulose acetate is commercially available with nominal acetyl values of either 32% or 40%. Membranes constructed from material at 32% acetyl value release drug from similar drug cores at a faster rate than do membranes constructed with the same amount of cellulose acetate by weight having a 40% acetyl value.

Preferred membrane materials include methacrylic ester copolymers, poly(ethyl acrylate, methyl methacrylate), for example EUDRAGIT® NE 30 D, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), for example, EUDRAGIT® RL or EUDRAGIT® RS, polymethyl methacrylate-methacrylic acid copolymers, cellulose acetate, and ethylcellulose, and combinations thereof.

One or more release orifices may be included through the semi-permeable membrane. This release orifice is included to allow passage of the active agent and the soluble excipients, either in addition to or as an alternative to the pores of the semi-permeable membrane. It can be used to further control the release rate of the active agent by varying its size. Typically, the size of the release orifice is between about 0.05mm and about 1.5mm, more narrowly between about 0.15mm and about 0.40mm.

The enteric coating is included to prevent the dissolution of the jacket and core in the stomach. It may consist of any pharmaceutically acceptable material which is gastric fluid resistant, that is a material soluble only in fluids with a pH greater than that of the stomach. Enteric coating materials include, but are not limited to, cellulose acetate phthalate NF, hydroxypropyl methylcellulose phthalate NF, polyvinyl acetate phthalate NF, and methacrylic acid copolymer NF. Thus, in a low pH environment, the enteric coating will be insoluble and hinder intrusion of water through the semi-permeable

membrane which could otherwise dissolve the delay jacket. It may be applied over the semi-permeable membrane using conventional film coating techniques known in the art, for example perforated pan coating.

Upon ingestion, the drug delivery device encounters the acidic gastric fluid, but remains intact because of the enteric coating. After the stomach pushes the device through the pylorus into the duodenum, the device is exposed to fluids of higher pH and the enteric coating dissolves. Once the semi-permeable membrane is exposed to these fluids, the device is activated. Water from the gastro-intestinal tract is imbibed through the membrane by diffusion and begins to selectively dissolve the delay jacket. As the soluble components of this delay jacket are selectively dissolved, they are released either through the membrane, or through the release orifice, until they are depleted. The delay jacket directly under the membrane prevents water from reaching the active drug core, thus providing the delayed release of the active agent. Once the delay jacket has been exhausted of soluble components, a suspension of insoluble material held in place by the membrane, continues to surround the active drug core. Eventually, the active core is reached by the water, increasing the pressure within the membrane as the core osmotic agents imbibe more and more water. As the drug is dissolved or suspended, this hydrostatic pressure forces the active agent through the membrane and/or through the release orifice to deliver the drug at a controlled rate. The release rate of the drug is based on the osmotic properties of the core, the solubility of the drug and excipients, and the water permeation rate through the membrane, and to a more limited extent, the viscosity of the solution or suspension, the suspension of material from the depleted delay jacket, and the size of the membrane pores or release orifice.

As an extension to the basic device, a further layer of active agent may be included to deliver an initial burst of active agent prior to the device reaching the colon. This active agent may be the same as or different from that within the core. The additional active agent layer may be applied over the enteric coating to deliver an immediate release of active agent. Alternatively, this additional layer may be applied under the enteric layer for release in the upper portion of the small intestine.

To deliver active agent intermittently, the basic device is altered by including an additional layer of active agent between the delay jacket and the membrane. This active agent layer comprises an active agent and may optionally include other pharmaceutically acceptable excipients including osmotic agents, lubricants, glidants, wetting agents,

binders, fillers, and suspending/thickening agents.

The following examples are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard.

Example 1 - Preparation of colonic delivery device

A colonic delivery device is prepared from the following ingredients:

INGREDIENTS	QUANTITY (mg)
Core	
Metoprolol Fumarate	190
Povidone, USP	22.2
Magnesium Stearate, NF	5.8
Delay jacket	
Dextrates, NF	148
Microcrystalline Cellulose, NF (PH101)	148
Hydroxyethyl Cellulose, NF (250H)	72.15
Magnesium Stearate, NF	1.85
Semi-permeable membrane	
Cellulose acetate, NF (398-10)	3.39
Cellulose acetate, NF (320 S)	23.49
Hydroxypropyl Methylcellulose, USP (15 cps)	1.56
Polyethylene Glycol, NF (3350)	1.56
Enteric coating	
Methacrylic Acid Copolymer, Type C, NF	24.72
Sodium Hydroxide, NF	0.36
Polyethylene Glycol 8000, NF	2.46
Talc, USP	2.46

Metoprolol fumarate and povidone are mixed together and granulated with an aqueous alcohol solution. The granulation is then dried, sized, and blended with magnesium stearate. The dried lubricated powder is compressed into tablet cores using conventional tabletting techniques.

Add the dextrates, microcrystalline cellulose, and hydroxyethyl cellulose to a planetary

mixer. Pass the magnesium stearate through a screen and add to mixer. Blend for approximately five minutes.

Add approximately 185 mg of the above mixture to the die cavity of a Colson single-punch tablet press fitted with a 14/32" tablet punch. Place one of the active cores onto the lower layer and add another 185 mg of the mixture. Compress the materials to form a press-coated, jacketed tablet.

Combine 456 mg methylene chloride and 114 mg methyl alcohol on a per tablet basis to form a solution. Dissolve the semi-permeable membrane ingredients in the solution using a propeller type mixer.

Spray coat the jacketed tablets with the above solution in a UniGlatt Coater using the following parameters:

Inlet Air Temperature	45-50°C
Atomizing Air Pressure	2.0 Bar
Spray Rate	15-25 ml/min

Drill the coated tablets with a 0.040" mechanical drill bit using a hand drill and laboratory arrangement.

For 100g of enteric coating dispersion, add 20g of methacrylic acid copolymer to 45.4g of water while mixing. In a second container, mix 0.3g of sodium hydroxide with 6.7g of water and add this mixture to the first container. In a third container, mix 2.0g of polyethylene glycol 8000 with 15.1g of water and add this to the first container. Continue to mix while adding 2.0g of talc and 8.5g of water to form a suspension.

Apply the above suspension to the coated tablets in a Glatt GC 300 12" Perforated Pan Coater using the following parameters:

Inlet Air Temperature	50-65°C
Atomizing Air Pressure	2.5 Bar
Nozzle Size and Type	1.1 mm, 35°
Spray Rate	15-22 ml/min

Example 2 - Dissolution test

The release rate of a tablet of Example 1 is determined using a two-hour presoak in 0.1N HCl and then a standard dissolution test using USP Rotating Basket and the following parameters:

Stir Rate	100 rpm
Wavelength	275 nm
Temperature	37°C
Medium	0.1 N HCL: 0-2 hr; phosphate buffer (pH=7.5): 2-24 hr

The results of the dissolution test are as follows:

Timepoint (hours)	Total Release (%Total)	Rate (%/hr)
0-2	<0.5	negligible
3-5	<0.5	negligible
6	1.7	1.3
7-8	16.5	7.4
9-10	33.6	8.6
11-12	48.3	7.4
13-14	61.0	6.4
15-18	76.2	3.8
19-24	82.7	1.1

Example 3 - Aqueously administrable semi-permeable membrane

A controlled release delivery device in which the semi-permeable membrane is applied aqueously is prepared from the following ingredients:

INGREDIENTS	QUANTITY
Core	per tablet (mg)
Acetaminophen	80.0
Malitol	98.0
Hydroxypropyl Methylcellulose, 15 cps	10.0
Polyethylene Glycol, 8000	10.0
Magnesium Stearate	2.0
Delay jacket	per tablet (mg)
Dextrates	409.0
Polyethylene Glycol, 8000	23.2
Hydroxypropyl Methylcellulose, 15cps	23.2
Magnesium Stearate	4.6
Semi-permeable membrane	per 1000g dispersion (g)
Cellulose Acetate Latex, 25% (prepared from cellulose acetate, USP)	121.2
Glyceryl Triacetate	45.5
Hydroxypropyl Methylcellulose, 15cps	3.3
Talc	3.3
Deionized Water	826.7

All core components are mixed together and sized. The mixture is then pressed into tablet cores using conventional tabletting techniques.

All delay jacket components are next sized and blended. The jacket is compressed around the drug core by partially filling a larger die cavity of a tablet punch with the jacket blend, placing a tablet core onto this layer and adding further jacket blend to fill the die cavity. The materials are then compressed to form a press-coated, jacketed tablet.

Stir together glyceryl triacetate, hydroxypropyl methylcellulose and talc to form a slurry. Add all of the deionized water while continuing to stir. When a uniform mixture of all components has formed, add the cellulose acetate latex and continue to mix the dispersion. Spray coat the jacket tablets to the desired membrane weight with this dispersion using a perforated pan coater with the following set points:

Nozzle Size	1.0mm Inlet Air
Temperature	68°C
Flowrate	135m^3/h
Pump Rate	10ml/min
Drum Speed	6.5rpm
Atomizing Air Pressure	2.0bar

Drill the coated tablets with a 0.25mm drill-bit to a depth of approximately 1mm.

The above coated tablets can be coated with an enteric dispersion as in example 1.

Example 4 - Preparation of an Intermittent Device

Ingredient	Quantity
Placebo Core	per tablet (mg)
dextrates	178.0
hydroxypropyl methylcellulose, 15 cps	10.0
polyethylene glycol 8000	10.0
magnesium stearate	2.0
Drug Sub-coat	per 1000g of solution (g)
phenylpropanolamine HCl	126.0
hydroxypropyl methylcellulose, 15 cps	25.0
polyethylene glycol 8000	10.0
deionized water	839.0

Delay Jacket	per tablet (mg)
dextrates	409.0
hydroxypropyl methylcellulose, 15 cps	23.2
polyethylene glycol 8000	23.2
magnesium stearate	4.6

Semipermeable Membrane	per 1000g of dispersion (g)
cellulose acetate 398-10	
(25% aqueous dispersion)	121.2
glyceryl triacetate	45.5
hydroxypropyl methylcellulose, 15 cps	3.3
talc	3.3
deionized water	826.7

Drug Over-coat	per 1000g of solution (g)
phenylpropanolamine HCl	98.0
hydroxypropyl methylcellulose, 15 cps	11.0
polyethylene glycol 8000	22.0
deionized water	869.0

All core components are mixed together and sized. The mixture is then pressed into tablet cores using conventional tabletting techniques.

To prepare the sub-coat, heat approximately one-third of the water to near boiling and add the hydroxypropyl methylcellulose followed by the polyethylene glycol with stirring. Remove from heat and add the Phenylpropanolamine HCl followed by the remaining water. Continue to stir until a clear solution is formed. Spray the drug solution onto the placebo cores in a perforated pan coater using the following set-points:

Inlet air temperature	68°C
Air volume flowrate	135m^3/h
Pump rate	18.9%
Drum speed	13.5 rpm
Atomizing air pressure	2.00bar
Nozzle size	0.8mm

Stop the process when approximately 32.1mg of drug sub-coat (corresponding to 22.5mg of Phenylpropanolamine HCl) has been applied to the tablets on an individual tablet basis.

The delay jacket and semipermeable membrane are applied as in example 5. The drug over-coat is applied in a manner similar to the drug sub-coat. The coating process is stopped when approximately 30 mg of over-coat is applied (corresponding to 22.5mg of Phenylpropanolamine HCl).

Drill the tablets using a 0.25mm drill bit and a mechanical arrangement to provide a release orifice.

CLAIMS:

1. Osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent which comprises:

a) a solid core containing an active agent;

b) a delay jacket coated over the core; and

c) a semi-permeable membrane coated over the delay jacket.

2. The device of claim 1, wherein the semi-permeable membrane comprises a release orifice.

3. The device of claim 1 or 2, wherein the delay jacket comprises an osmotic agent.

4. The device of claim 3, wherein the delay jacket further comprises at least one excipient selected from the group consisting of a binder, a hygroscopic suspending or thickening agent, and a tablet lubricant.

5. The device of any one of claims 1 to 4, wherein the semi-permeable membrane comprises a compound selected from the group consisting of methacrylic ester copolymers, poly(ethyl acrylate, methyl methacrylate), poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), polymethyl methacrylate-methacrylic acid copolymers, cellulose acetate, ethylcellulose, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate.

6. The device of any one of claims 1 to 5, further comprising an enteric coating over the semi-permeable membrane.

7. The device of claim 6, wherein the enteric coating is selected from the group consisting of cellulose acetate phthalate NF, hydroxypropyl methylcellulose phthalate NF, polyvinyl acetate phthalate NF, and methacrylic acid copolymer NF.

8. A process for the preparation of an osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent which comprises:

a) forming a solid core containing an active agent;

b) coating said core with a delay jacket; and

c) coating said core with a semi-permeable membrane.

9. The process of claim 8, further comprising applying a release orifice to the semi-permeable membrane.

10. The process of claim 8 or 9, further comprising applying an enteric coating over the semi-permeable membrane.

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(19) (CA) **CANADIAN PATENT** (12)

(54) Long-Active Drug Formulations Comprising Galanthamine for Treatment of Alzheimer`s Disease

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A B S T R A C T

Long-acting Galanthamine formulation is prepared by coating particles of drug with polyvinyl pyrrolidone, sizing the particles and incorporating them into a capsule or tablet.

The present invention relates to long-acting formulations for treatment of Alzheimer's disease and related dementias.

United States Patent No. 4,663,318 (Davis issued May 5, 1987) describes the use of galanthamine and its salts for treatment of Alzheimer's disease and related dementias. The possibility of using a long-acting formulation of the drug is suggested therein.

According to the present invention, there is provided a sustained release formulation in the form of a tablet or capsule for oral administration for treatment of Alzheimer's disease and related dementias comprising particles of galanthamine or a pharmaceutically acceptable salt thereof.

A preferred compound of the above formula is galanthamine hydrobromide.

Suitable pharmaceutically acceptable coating agents include polyvinyl pyrrolidone.

A particularly useful method for producing formulations of the present invention is to coat the drug substance with polyvinyl pyrrolidone alcohol solution to form granules. These granules are the^passed thru a sieve machine to obtain various sizes of granules. A determined amount of each of different size granules are mixed with excipient such as hydroxypropyl methyl cellulose, ethyl cellulose, starch, silicon dioxide, and with a lubricant such as magnesium stearate or polyethylene glycol to form a tablet or to be incorporated into a capsule.

The final drug preparation is tested for dissolution profile in addition to the general testing requirements. A useful dissolution profile for a sustained release preparation according to the present invention is:

Active drug	1-2 hours	10-20%
dissolved	2-4 hours	20-40%
in gastric	4-8 hours	40-80%
juice	12 hours	balance

Typically the sizing of the particles incorporated into a table or capsule will be chosen so as to produce a sustained release over a four to twelve hour period, for example, over a eight hour period.

Typically capsules or tablets according to the present invention contain a quarter to a half of the typical daily dose of drug, although dosage units outside this range are also possible. Such daily doses are normally for 10 to 2000 mg per day, more typically 100 to 600 mg per day. Typically, therefore, tablets or capsules comprise 25 to 250 mg of active compound.

1. A sustained release formulation for oral administration in the form of a tablet or capsule for treatment of Alzheimer's disease and related dementias comprising particles of galanthamine or a pharmaceutically acceptable salt thereof, said particles being coated with a pharmaceutically acceptable coating agent that is soluble in the intestinal tract, the thickness of the coatings varying between individual particles, a plurality of said particles having various coating thickness chosen so as to result, after administration, in release of the drug from its coated particles at different times.

2. A sustained release formulation as claimed in claim 1 wherein said particles comprise galanthamine hydrobromide.

3. A sustained release formulation as claimed in claim 1 wherein said coating material is polyvinyl pyrrolidone.

4. A sustained release formulation as claimed in claim 1 containing 25 to 250 mg of active compound.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente

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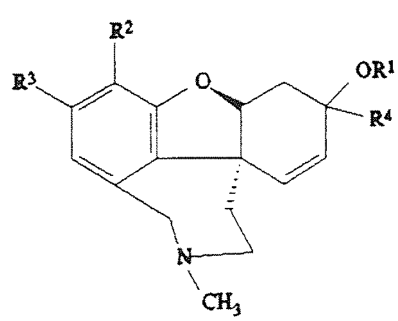
(54) **Galanthamine derivatives, a process for their preparation and their use as medicaments.**

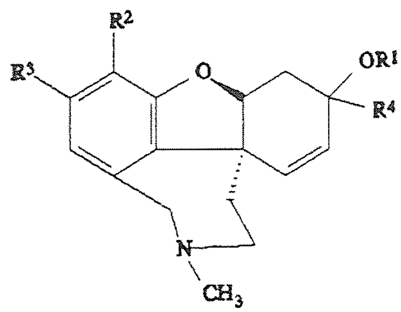
(57) This application relates to compounds of the formula



wherein R^1, R^2, R^3 and R^4 are defined within, which compounds are useful for the treatment of memory dysfunction characterized by decreased cholinergic function, pharmaceutical compositions containing the compounds and methods for making and using the compounds.

EP 0 653 427 A1

This application relates to compounds of the formula (I)



(I)

wherein

- R^1 is hydrogen, $(C_1\text{-}C_{12})$alkylcarbonyl, $(C_1\text{-}C_{12})$alkoxycarbonyl, mono$(C_1\text{-}C_{12})$alkylaminocarbonyl or di$(C_1\text{-}C_8)$alkylaminocarbonyl;
- R^2 is hydrogen, $(C_3\text{-}C_{12})$alkenylcarbonyloxy,$(C_3\text{-}C_{12})$cycloalkylcarbonyloxy, $(C_3\text{-}C_{12})$-cycloalkylaminocarbonyloxy, $(C_3\text{-}C_{12})$alkynylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_{12})$-alkylcarbonyloxy, oxygen containing heterocyclyloxy, oxygen containing heterocyclylcarbonyloxy, sulfur containing heterocyclyloxy, sulfur containing heterocyclylcarbonyloxy, nitrogen containing heterocyclyloxy, nitrogen containing heterocyclylcarbonyloxy, haloalkylsulfonyloxy, $(C_1\text{-}C_6)$-alkylsilyloxy;
- R^3 is hydrogen, halo or $(C_1\text{-}C_4)$alkyl;
- R^4 is hydrogen or $(C_1\text{-}C_6)$alkyl;

with the proviso that R^1 and R^2 are not both hydrogen when R^3 and R^4 are hydrogen;

all geometric, and optical and stereoisomers thereof, or a pharmaceutically acceptable addition salt thereof;

which are useful for alleviating various memory dysfunctions such as found in Alzheimer's disease.

This invention also provides a pharmaceutical composition useful for alleviating various memory dysfunctions characterized by decreased cholinergic function which comprises a compound of the invention in an amount sufficient to affect cholinergic function and a pharmaceutically acceptable carrier.

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and appended claims.

The term "alkyl" shall mean a straight or branched alkyl group of the stated number of carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, t-butyl, and straight and branched chain pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and dodecyl.

The term "halo" shall mean chloro, fluoro, bromo and iodo.

The term "aryl" shall mean phenyl having 0, 1, 2 or 3 substituents independently selected from the group of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylcarbonyl, halo or trifluoromethyl.

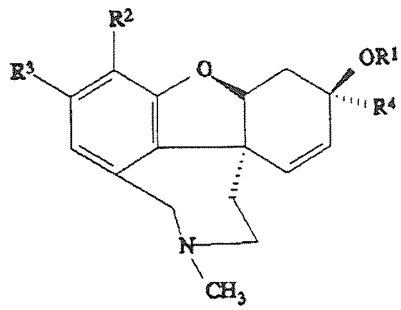
The term "cycloalkyl" shall mean a cycloalkyl group of from 3 to 12 carbon atoms such as for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclododecyl and including multiple ring alkyls such as for example, norbornanyl, adamantyl, cis-bicyclo[3.3.0]octanyl, camphoryl, oxotricyclo-[2.2.1.0^{2,6}]heptane-7-yl and 3-noradamantyl.

The term "nitrogen-containing heterocycle" shall mean a 5 or 6 membered saturated or partially unsaturated ring, optionally fused to another saturated, unsaturated or aromatic ring, having at least one nitrogen atom which is also bonded to the additional portion of the molecule. Examples include morpholine, tetrahydroisoquinoline, piperidine, pyrrolidine, pyridine and the like.

The term "oxygen-containing heterocycle" shall mean a 5 or 6 membered saturated or partially unsaturated ring, optionally fused to another saturated, unsaturated or aromatic ring, having at least one oxygen atom which is also bonded to the additional portion of the molecule. Examples include furan and tetrahydrofuran and the like.

The term "sulfur-containing heterocycle" shall mean a 5 or 6 membered saturated or partially unsaturated ring, optionally fused to another saturated, unsaturated or aromatic ring, having at least one sulfur atom which is also bonded to the additional portion of the molecule. Examples include thiophene and the like.

In a preferred embodiment are compounds of the formula (II)



(II)

wherein

R^1 is hydrogen, $(C_1\text{-}C_{12})$alkylcarbonyl, $(C_1\text{-}C_{12})$alkoxycarbonyl;

R^2 is hydrogen, $(C_3\text{-}C_{12})$alkenylcarbonyloxy, $(C_3\text{-}C_{12})$alkynylcarbonyloxy, $(C_3\text{-}C_{12})$-cycloalkylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_{12})$alkylcarbonyloxy, $(C_3\text{-}C_{12})$-cycloalkylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkylaminocarbonyloxy, halo$(C_1\text{-}C_6)$alkylsulfonyloxy, $(C_1\text{-}C_6)$-alkylsilyloxy, pyridyloxy, thiomorpholinocarbonyloxy, furanylcarbonyloxy, thienylcarbonyloxy, tetrahydrofuranylcarbonyloxy, furanyloxy, thienyloxy, pyrrolidinylcarbonyloxy, tetrahydrofuranyloxy, piperadinylcarbonyloxy, azepincarbonyloxy, morpholinocarbonyloxy or tetrahydroisoquinolinylcarbonyloxy;

R^3 is hydrogen or halo;

R^4 is hydrogen or $(C_1\text{-}C_6)$alkyl;

with the proviso that R^1 and R^2 are not both hydrogen when R^3 and R^4 are hydrogen;

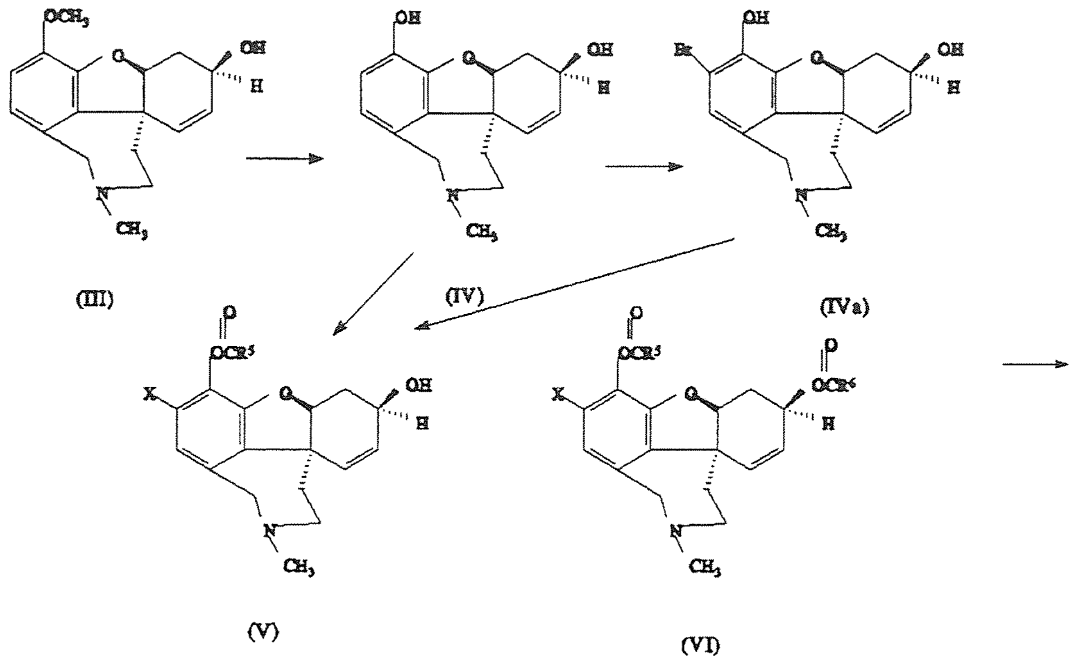
and all geometric, optical and sterioisomers and pharmaceutically acceptable addition salts thereof.

More preferably R^1 is hydrogen, $(C_1\text{-}C_{12})$alkylcarbonyl or $(C_1\text{-}C_{12})$alkoxycarbonyl; R^2 is $(C_3\text{-}C_{12})$-alkenylcarbonyloxy, $(C_3\text{-}C_{12})$alkynylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_{12})$-alkylcarbonxyloxy, pyridyloxy, furanyloxy, morpholinocarbonyloxy or tetrahydroisoquinolylcarbonyloxy; R^3 is hydrogen or bromine; and R^4 is hydrogen or methyl.

Most preferably R^1 is hydrogen, R^2 is cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclohexylcarbonyloxy, methylcyclohexylcarbonyloxy, adamantylcarbonyloxy, adamantylmethylcarbonyloxy, 2-methylpropenylcarbonyloxy, 2-propynylcarbonyloxy, cycloheptylaminocarbonyloxy, cyclohexylaminocarbonyloxy, morpholinocarbonyloxy or tetrahydroisoquinolylcarbonyloxy; and R^3 and R^4 are hydrogen.

The compounds of the invention are prepared from the appropriate optical isomer of galanthamine as described more fully below and shown in Scheme I.

SCHEME I



The intermediate 6-demethylgalanthamine of Formula IV, a known compound was prepared in a novel process by treating the galanthamine of Formula III with an alkylthio salt of sodium, potassium, lithium or cesium, preferably (C_1-C_4)alkylthio salts of sodium and lithium, most preferably EtSLi, or EtSNa. The reaction is typically carried out in a polar nonprotic solvent such as dimethylformamide (DMF) or N-methylpyrrolidone (NMP) or a protic solvent such as butanol or pentanol, preferably DMF or NMP at from about 80°C to about 135°C, preferably from about 90°C to about 125°C.

The compound of Formula VI wherein R^5 is (C_3-C_{12})cycloalkylaminocarbonyl is prepared by treating the compound of Formula IV with the appropriate isocyanato compound R^4NCO. The reaction is carried out in an aprotic solvent such as, for example, tetrahydrofuran in the presence of base such as, for example, potassium carbonate at from about -10°C to about 30°C for from about 0.5 hours to about 4 hours.

In the case where R^5 is cycloalkylcarbonyl, alkenylcarbonyl or alkynylcarbonyl, the compound of Formula V is typically reacted with an appropriate carboxylic anhydride in the presence of a base such as 4-dimethylaminopyridine (DMAP) or carboxylic acid chloride in the presence of a base such as 1,8-diazabiscyclo[5.4.0]undec-7-ene (DBU). The reactions are typically carried out in a non-protic solvent such as, for example, chloroform at from about 0°C to about 50°C, preferably from about 15°C to about 30°C.

In the case where R^5 is pyridyl or other heterocycle, the compound of Formula V is typically reacted with an appropriate halopyridine or other haloheterocycle in the presence of base such as for example potassium t-butoxide. The reaction is typically carried out in a non-protic polar solvent such as, for example, dimethylformamide at from about room temperature to about 150°C, preferably about 110°C.

In the case where R^5 is alkylsilyl, the compound of Formula V is typically reacted with the appropriate alkylsilyl halide at from about 0°C to about 80°C, preferably at about room temperature. The reaction is typically carried out in a non-protic solvent such as dimethylformamide or tetrahydrofuran.

In the case where R^5 is haloalkylsulfonyl, the compound of Formula V is typically reacted with the appropriate sulfonic acid anhydride in a solvent such as pyridine. Alternatively the reaction can be carried out at about -60°C to about -50°C in dichloromethane or chloroform in the presence of a base such as diisopropylethylamine.The reaction is typically carried out at from about -10°C to about 50°C, preferably from about 0°C to about room temperature.

The compound of Formula VI can be prepared from the compound of Formula V. In the case where R^6 is alkylamino or arylamino, a solution of the appropriate isocyanate and the compound V in a nonprotic solvent such as tetrahydrofuran in a sealed tube at from about 55°C to about 85°C for from about 24 hours to about 120 hours, preferably at from about 60°C to about 70°C for from about 60 hours to about 80

hours.

In the case where R^6 is alkyl or aryl, the compound of Formula V is reacted with the appropriate carboxylic acid or anhydride under the conditions described above to obtain the compound of Formual VI.

In the case where X is Br, the compound of Formula IV is treated with bromine in the presence of an amine such as t-butylamine to obtain the brominated compound. The bromine is first added to the t-butylamine at from about -20°C to about -30°C, then the reaction mixture is cooled to about -80°C to about -70°C and the galanthamine compound is added. The reaction is typically carried out in a nonpolar organic solvent such as for example toluene. Following addition of galanthamine the mixture is allowed to warm from about -80°C to about room temperature over from about 6 hours to about 10 hours, preferably about 8 hours.

In the case where R^2 of Formula I is hydrogen, the haloalkylsulfonyl compound of Formula V is typically reacted with palladium acetate and triphenylphosphine followed by triethylamine and formic acid. The reaction is typically carried out in a polar solvent such dimethylformamide at from about room temperature to about 100°C, at about 60°C to about 70°C.

In the case where R^4 of Formula I is alkyl, typically the appropriate narwedine compound is reacted with the appropriate alkylmagnesium bromide in the presence of cerium (III) chloride. The reaction is typically carried in a non-protic solvent such as tetrahydrofuran at from about -10°C to about room temperature, preferably at about 0°C.

The compounds of Formula I of the present invention can be used for the treatment of various memory dysfunctions characterized by decreased cholinergic function, such as Alzheimer's disease. The compounds of the present invention are advantageous because they are less toxic and/or more potent than the related compounds known in the art. In addition, the 6-O-demethyl ester and carbonate derivatives of this invention can cleave to yield 6-O-demethylgalanthamine, a known acetylcholinesterase inhibitor.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

The ability to inhibit acetylcholinesterase was determined by the photometric method of Ellman et al., Biochem. Pharmacol. 7,88 (1961). Results of acetylcholinesterase inhibition for some of the compounds of this invention are presented in Table I along with those for reference compounds.

TABLE I

Acetylcholinesterase Inhibition Assay	
Compound	IC_{50} uM CHE I
(6-O-Demethyl)-6-O-(1,2,3,4-tetrahydroisoquinolin-2-yl)-carbonyl]-galanthamine hydrochloride	0.0009
Tacrine	0.32

This utility can also be ascertained by determining the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay. In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed from the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

If scopolamine, an anticholinergic that is known to cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is blocked by an active test compounds, resulting in a greater interval before re-entry into the dark compartment.

The test results are expressed as the percent of a group of animals in which the effect of scopolamine is blocked, as manifested by an increased interval between being placed in the test chamber and re-entering the dark compartment. Results of Dark Avoidance Assay for some of the compounds of this invention are presented in Table II along with a result for a reference compounds.

TABLE II

Example No.	SDDA Dose (mg/kg, s.c.)	Percent of Animals with Scopolamine Induced Memory Deficit Reversal
(6-O-Demethyl)-6-O-(1,2,3,4-tetrahydroisoquinolin-2-yl)-carbonyl]-galanthamine hydrochloride	0.003	27
Tacrine	0.31	33

Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compounds, but may be varied depending upon the particular form and may conveniently be between 5% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0 - 200 milligrams of active compound.

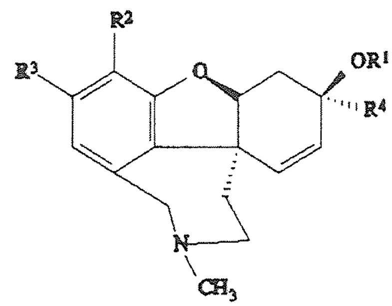
The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin: an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above-type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1 % of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present inventions are prepared so that a parenteral dosage unit contains between 0.5 to 200 milligrams of active compound.

The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents, such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates; citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral multiple dose vials may be of glasser plastic.

The following Table III and examples will further illustrate this invention but are not intended to limit it in any way. In Table III typical compounds of the instant invention are listed. The melting points are of hydrochloride salts unless otherwise indicated. Following Table III, representative illustrative preparations of compounds of the invention are described.

TABLE III



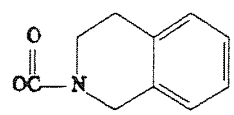
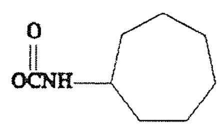
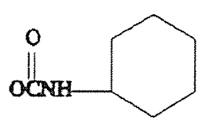
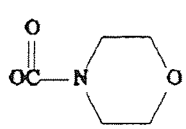
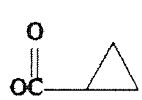
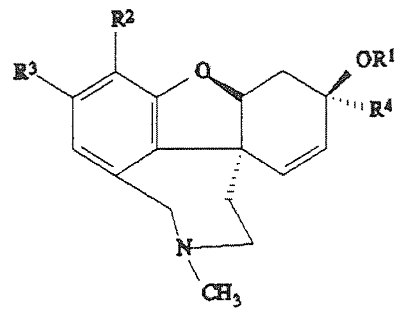
Ex. No.	R^1	R^2	R^3	R^4	m.p.°C
1	H	OH	H	H	225-229*[a]
2	H		H	H	258-260
3	H		H	H	224-226
4	H		H	H	238-240
5	H	OH	Br	H	138-141[a]
6	H		H	H	263-265d
7	H		H	H	244-245d

TABLE III



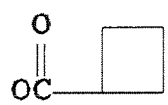
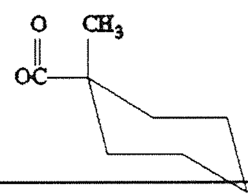
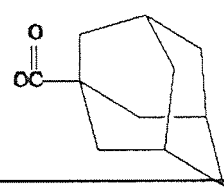
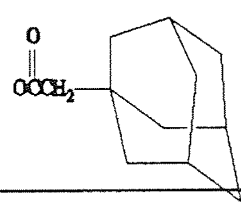
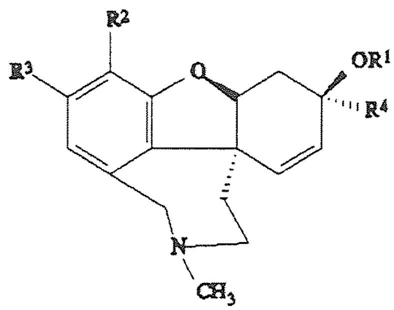
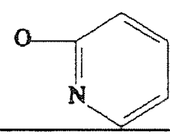
Ex. No.	R^1	R^2	R^3	R^4	m.p.°C
8	H		H	H	200-203
9	H		H	H	256-258d
10	H		H	H	258-260d
11	H		H	H	253-255
12	H	$OC(=O)CH=C(CH_3)_2$	H	H	247d
13	H	$-OC(=O)C\equiv CCH_3$	H	H	191-195

TABLE III



Ex. No.	R^1	R^2	R^3	R^4	m.p.°C
14	H		H	H	250-251 d
15	H	$OS(=O)_2CF_3$	H	H	219-220
16	H	$OSi(CH_3)_2C(CH_3)_3$	H	H	199 d
17	H	$OSi(CH_2CH_3)_3$	H	H	128-130
18	H	$OSi(CH(CH_3)_2)_3$	H	H	235 d
19	H	$OSi(CH_3)_3$	H	H	173-174
20	H	H	H	H	242-244
21	H	OCH_3	H	CH_3	237-240

Lit. m.p. 220-222

' isolated as free base

EXAMPLE 1

6-O-Demethylgalanthamine

To a stirred solution of 20 ml of dry DMF at -40° under nitrogen was added 0.57 ml (0.48 g) of ethanethiol. The mixture was stirred for several minutes at -40° to -30° after which 2.84 ml of 2.5 M BuLi in hexanes was added slowly by syringe at -40° to -50°. The solution was then allowed to warm to room temperature over 15 minutes, heated to 50° under aspirator vacuum and again cooled to 30°. To the solution was added a solution of 0.57 g of galanthamine in 5.7 ml of dry DMF. The solution was stirred at 95-100° for 2 hours and subsequently at 100-105° for 3 hours, allowed to cool to room temperature and concentrated to an oil. The oil was dissolved in chloroform, shaken with NH_4Cl, made basic with aq $NaHCO_3$ and extracted four times with $CHCl_3$. The pH of the aqueous layer was then adjusted to 9-10 with

NH_4OH and again extracted four times with chloroform. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to an oil. The oil was dissolved in degassed 5% methanol/chloroform and flash chromatographed on silica gel eluting with the same solvent system followed by 10% methanol/chloroform to provide a beige solid. The material was dissolved in acetone and allowed to crystallize overnight to provide 0.298 g of 6-O-demethylgalanthamine, m.p. 225-229°.

ANALYSIS:			
Calculated for $C_{16}H_{19}NO_3$:	70.31%C	7.01%H	5.12%N
Found:	70.14%C	7.29%H	4.96%N

EXAMPLE 2

(6-O-Demethyl)-6-O-(1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]-galanthamine hydrochloride

To a stirred suspension of 0.494 g of 6-O-demethylgalanthamine in 7 ml of dry dichloromethane was added 0.311 g of 1,1'-carbonyldiimidazole. The mixture was stirred at room temperature for 1 hour, cooled in an ice bath and 0.35 ml of acetic acid was added followed by 0.27 ml of 1,2,3,4-tetrahydroisoquinoline. The mixture was allowed to warm to room temperature and stirred at room temperature for 15 hours. The solution was cooled in an ice bath, poured into cold saturated $NaHCO_3$, extracted with dichloromethane, washed with water and concentrated to an oil. The material was dissolved in ethyl acetate/ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 0.346 g of a white solid, m.p. 258-260°.

ANALYSIS:			
Calculated for $C_{26}H_{28}N_2O_4 \cdot HCl$:	66.59%C	6.23%H	5.97%N
Found:	66.21%C	6.26%H	5.90%N

EXAMPLE 3

6-O-Demethyl-6-O-(cycloheptylaminocarbonyl)galanthamine hydrochloride

To a mixture of 0.81 g of 6-O-demethylgalanthamine and 0.82 g of milled potassium carbonate was added 13.5 ml of dry THF via a syringe. The suspension was cooled to 0°C after which 0.60 ml of cycloheptyl isocyanate was added slowly by syringe. The mixture was allowed to stir at 0°C for 30 minutes and at room temperature for 45 minutes. The solution was poured onto a flash chromatography column, packed with silica gel and 3% methyl alcohol:chloroform, and eluted with the same solvent followed by 5% methyl alcohol:chloroform. The product-containing fractions were combined and concentrated to provide a white solid weighing 1.28 g. The solid was dissolved in dichloromethane, diluted with ethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 1.07 g of 6-O-demethyl-6-O-(cycloheptylaminocarbonyl)galanthamine hydrochloride, m.p. 224-226°C.

ANALYSIS:			
Calculated for $C_{24}H_{30}N_2O_4 \cdot HCl$:	64.20%C	7.41%H	6.24%N
Found:	63.78%C	7.47%H	6.17%N

EXAMPLE 4

6-O-Demethyl-6-O-(cyclohexylaminocarbonyl)galanthamine hydrochloride

To a stirred suspension of 0.8 g of 6-O-demethylgalanthamine, 0.8 g of milled potassium carbonate and 14 ml of THF in an ice bath was added 0.48 ml of cyclohexylisocyanate. The suspension was stirred at ice

bath temperature for 1/2 hour and at room temperature for 1/2 hour. The mixture was then filtered onto a flash silica gel column packed with 3% methanol/chloroform and flash chromatographed eluting with the same solvent system followed by 5% methanol/chloroform. Concentration of the product-containing fractions provided an oil which was dissolved in ether and the hydrochloride salt precipitated by addition of ethereal HCl. The material was isolated by filtration and dried to provide 0.637 g of a white solid. Trituration/crystallization from ethanol provided analytically pure 6-O-demethyl-6-O-(cyclohexylaminocarbonyl)galanthamine hydrochloride, m.p. 238-240 °C.

ANALYSIS:			
Calculated for $C_{23}H_{30}N_2O_4 \cdot HCl$:	63.51%C	7.18%H	6.44%N
Found:	63.32%C	7.18%H	6.28%N

EXAMPLE 5

7-Bromo-6-O-demethylgalanthamine

To a stirred solution of 1.38 ml (0.966 g) of t-butylamine in 36 ml of azeotripically dried toluene at -20 to -30 °C was added dropwise 0.34 ml (1.05 g) of bromine such that the temperature remained between -20 to -30 °C. The solution was then cooled to -70 to -75 °C and a solution of 3.0 g of 6-demethylgalanthamine in 15 ml of DMF was added slowly such that the temperature did not rise above -70 °C. The solution was stirred for 2 hours at -70 to -78 °C and subsequently allowed to warm slowly to room temperature over 6 hours. The solution was again cooled to 0 °C, poured into ice/$NaHCO_3$/water, and extracted with chloroform. The aqueous fraction was saturated with NaCl and extracted 3 times with chloroform. The chloroform extracts were dried (Na_2SO_4), filtered and concentrated to an oil which was purified by HPLC, employing a Water Prep 500 Instrument and eluting with 3% methanol/chloroform, followed by 5% methanol/chloroform. The pure product-containing fractions were combined and concentrated to provide 1.83 g (47.3% based on 6-demethylgalanthamine, 78.9% based on bromine, the limiting reagent). Crystallization from acetone provided analytically pure 7-bromo-6-O-demethyl galanthamine, m.p. 138-141 °C.

ANALYSIS:			
Calculated for $C_{16}H_{18}BrNO_3$:	54.56%C	5.15%H	3.98%N
Found:	54.62%C	5.50%H	3.61%N

EXAMPLE 6

6-O-Demethyl-6-O-(morpholinocarbonyl)galanthamine hydrochloride

To a stirred suspension of 0.80 g of 6-O-demethylgalanthamine in 11.2 ml of dichloromethane was added 0.50 g of 1,1'-carbonyldiimidazole. The mixture was stirred at room temperature for 1 hour and cooled in an ice bath. To the mixture was added 0.57 ml of acetic acid followed by 0.31 ml of morpholine at 0 °C. The mixture was allowed to stir at room temperature for 3.5 hours and cooled once again to 0 °C. The mixture was poured into a cold saturated solution of sodium bicarbonate and extracted twice with chloroform. The organic layers were combined, dried over Na_2SO_4, filtered and and concentrated to a yellow oil. The oil was dissolved in 3% methanol:chloroform and pipetted onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The product-containing fractions were combined and concentrated to provide 0.86 g of an oil, which was dissolved in ethyl ether:chloroform and the hydrochloride salt was precipitated by addition of ethereal hydrogen chloride to provide 0.65 g of 6-O-demethyl-6-O-(morpholinocarbonyl)-galanthamine hydrochloride as a white solid. The solid was recrystallized from acetonitrile:isopropyl alcohol, to provide material of m.p. 263-265 °C (dec).

ANALYSIS:			
Calculated for $C_{21}H_{26}N_2O_5 \cdot HCl$:	59.64%C	6.44%H	6.62%N
Found:	59.60%C	6.09%H	6.72%N

EXAMPLE 7

6-O-Demethyl-6-O-(cyclopropanecarbonyl)galanthamine hydrochloride

To a stirred mixture of 0.80 g (2.92 mmol) of 6-O-demethylgalanthamine in 8 ml of dry chloroform was added 0.44 ml (2.94 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was stirred at 0°C for 10 minutes after which was added 0.29 ml (3.19 mmol) of cyclopropanecarbonyl chloride by syringe. The mixture was warmed to room temperature and stirred at this temperature for 2 hours, poured into a cold saturated solution of sodium bicarbonate and extracted twice with chloroform. To the aqueous layer was added sodium chloride after which it was extracted twice with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to provide a yellow oil. The oil was dissolved in chloroform, pipetted onto a flash chromatography column packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system followed by 5% methanol:chloroform. The pure, product-containing fractions were combined and concentrated to provide 0.76 g (2.23 mmol, 76%) of a white solid. The solid was dissolved in diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 0.56 g (1.65 mmol; 56%) of 6-O-demethyl-6-O-(cyclopropanecarbonyl)galanthamine hydrochloride , m.p. 244-245°C (dec.).

ANALYSIS:			
Calculated for $C_{20}H_{23}NO_4 \cdot HCl$:	63.57%C	6.40%H	3.71%N
Found:	63.29%C	6.39%H	3.74%N

EXAMPLE 8

6-O-Demethyl-6-O-(cyclobutanecarbonyl)galanthamine hemihydrate hydrochloride

To a stirred suspension of 1.00 g (3.66 mmol) of 6-O-demethylgalanthamine in 8.0 ml of dry chloroform was added 0.55 ml (3.67 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The suspension was stirred at 0°C for 10 minutes after which was added 0.47 g (4.00 mmol) of cyclobutanecarbonyl chloride. The reaction mixture was warmed to room temperature and stirred at this temperature for 3 hours after which it was poured into a cold, saturated solution of sodium bicarbonate. The mixture was extracted once with chloroform and the aqueous layer was treated with sodium chloride and extracted twice with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to an oil. The oil was dissolved in chloroform and pipetted onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The appropriate fractions were combined and concentrated to provide a solid weighing 0.71 g (1.77 mmol; 48%). The solid was dissolved in diethyl ether and chloroform and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to give 6-O-demethyl-6-O-(cyclobutanecarbonyl)galanthamine hemihydrate hydrochloride, m.p. 200-203°C.

ANALYSIS:			
Calculated for $C_{21}H_{25}NO_4 \cdot 0.5H_2O \cdot HCl$:	62.92%C	6.79%H	3.49%N
Found:	62.68%C	6.84%H	3.43%N

EXAMPLE 9

6-O-Demethyl-6-O-(1-methylcyclohexanecarbonyl)galanthamine hydrochloride

To a stirred suspension of 0.37 g (2.63 mmol) of 1-methyl-1-cyclohexanecarboxylic acid in 1.0 ml of chloroform was added 0.54 g (2.61 mmol) of 1,3-dicyclohexylcarbodiimide dissolved in 1.0 ml of chloroform, followed by 0.71 g (2.62 mmol) of 6-O-demethylgalanthamine, and 3.17 g (2.59 mmol) of 4-dimethylaminopyridine dissolved in 1.5 ml of chloroform. The mixture was stirred at room temperature overnight after which it was poured into a cold saturated solution of sodium bicarbonate and extracted twice with chloroform. To the aqueous layer was added sodium chloride after which it was extracted twice with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to a yellow oil. The oil was dissolved in chloroform, filtered onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The pure, product-containing fractions were combined and concentrated to a white solid weighing 0.49 g (1.25 mmol; 48%). The solid was dissolved in diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 6-O-demethyl-6-O-(1-methylcyclohexanecarbonyl)galanthamine hydrochloride, m.p. 256-258d.

ANALYSIS:			
Calculated for $C_{24}H_{31}NO_4 \cdot HCl$:	66.42%C	7.43%H	3.23%N
Found:	66.66%C	7.47%H	3.17%N

EXAMPLE 10

6-O-Demethyl-6-O-[(adamantan-1-yl)carbonyl]galanthamine hydrochloride

To a stirred solution of 0.59 g (3.28 mmol) of 1-adamantanecarboxylic acid in 1.5 ml of chloroform was added 0.68 g of 1,3-dicyclohexylcarbodiimide dissolved in 0.5 ml of chloroform, followed by 0.90 g (3.28 mmol) of 6-O-demethylgalanthamine, and 0.40 g of 4-dimethylaminopyridine dissolved in 0.5 ml of chloroform. The reaction mixture was allowed to stir at room temperature for 5 hours after which it was filtered onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The pure, product-containing fractions were combined and concentrated to a white solid weighing 0.67 g (1.54 mmol; 47%). The solid was dissolved in chloroform and diluted with diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride. Recrystallization from acetonitrile:isopropanol followed by drying at 78 °C, under high vacuum, provided 6-O-demethyl-6-O-[(adamantan-1-yl)carbonyl]galanthamine hydrochloride, m.p. 258-260 °C (dec).

ANALYSIS:			
Calculated for $C_{27}H_{33}NO_4 \cdot HCl$:	68.70%C	7.26%H	2.97%N
Found:	68.46%C	7.48%H	2.87%N

EXAMPLE 11

6-O-Demethyl-6-O-[(adamantan-1-yl)methylcarbonyl]galanthamine hydrochloride

To a stirred suspension of 0.71 g (3.67 mmol) of 1-adamantaneacetic acid in 2.5 ml of chloroform was added 0.75 g (3.67 mmol) of 1,3-dicyclohexylcarbodiimide dissolved in 1.0 ml of chloroform, followed by 1.00 g (3.66 mmol) of 6-O-demethyl-galanthamine in 2.0 ml of chloroform and 0.45 g (3.67 mmol) of dimethylaminopyridine. The mixture was stirred for 2 hours after which it was filtered onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The appropriate fractions were combined and concentrated to a white solid weighing 1.16 g (2.58 mmol; 70%). The solid was dissolved in diethyl ether

and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 0.90 g (1.86 mmol; 51%) of 6-O-demethyl-6-O-[(adamantan-1-yl)methylcarbonyl]galanthamine hydrochloride, m.p. 253-255 °C (dec).

ANALYSIS:			
Calculated for $C_{28}H_{35}NO_4 \cdot HCl$: Found:	69.19%C 68.93%C	7.47%H 7.51%H	2.88%N 2.85%N

EXAMPLE 12

6-O-Demethyl-6-O-(2-methyl-1-propenylcarbonyl)galanthamine hydrochloride

To a cold solution of 6-O-demethylgalanthamine (2.0 g, 0.007 mole), triethylamine (1.10 ml, 0.007 mole) and 4-dimethylaminopyridine (0.01 g, 0.0001 mole) in 70 ml of dichloromethane, was added dropwise a solution of 3,3-dimethylacryloyl chloride (0.8 ml, 0.007 mole) in 10 ml of dichloromethane. After stirring at ambient temperature for 3 hours, the mixture was added to a silica gel column and eluted with 3% methanol/dichloromethane via HPLC. The desired fractions were combined and then evaporated to give a white solid, 1.6 g (64%), m.p. 74-75 °C. A solution of the solid in ether was adjusted to pH 1 with ethereal-HCl, and the resultant white solid was collected and dried to give 1.2 g (45%) of product, m.p. 247 °C (dec.).

ANALYSIS:			
Calculated for $C_{21}H_{25}NO_4 \cdot HCl$: Found:	64.36%C 64.18%C	6.69%H 6.73%H	3.57%N 3.51%N

EXAMPLE 13

6-O-Demethyl-6-O-(propynylcarbonyl)galanthamine hydrochloride

To a stirred mixture of 0.61 g (7.31 mmol) of 2-butynoic acid in 3.0 ml of chloroform was added 1.51 g (7.31 mmol) of 1,3-dicyclohexylcarbodiimide dissolved in 2.0 ml of chloroform, followed by 1.99 g (7.31 mmol) of 6-O-demethylgalanthamine, 2.0 ml of chloroform, and 0.09 g (0.73 mmol) of 4-dimethylaminopyridine dissolved in 0.5 ml of chloroform. The reaction mixture was stirred at room temperature for 0.5 hours after which it was poured into a cold, saturated solution of sodium bicarbonate and extracted once with chloroform. To the aqueous layer was added sodium chloride after which it was extracted twice with chloroform, and the combined chloroform extracts, dried over sodium sulfate, filtered, and concentrated to a brown oil. The oil was dissolved in chloroform, filtered onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform, and eluted with the same solvent system, followed by 5% methanol:chloroform. The pure, product-containing fractions were combined and concentrated to a yellow oil weighing 1.84 g (5.41 mmol; 74%). The oil was dissolved in diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 1.00 g (2.67 mmol; 37%) of 6-O-demethyl-6-O-(propynylcarbonyl)galanthamine hydrochloride, m.p. 191-195 (dec.).

ANALYSIS:			
Calculated for $C_{20}H_{21}NO_4 \cdot HCl$: Found:	63.91%C 63.38%C	5.90%H 5.73%H	3.73%N 3.59%N

EXAMPLE 14

6-O-Demethyl-6-O-(pyridin-2-yl)galanthamine hydrochloride

A mixture of 2.00 g (7.33 mmol) of 6-O-demethylgalanthamine and 822.1 mg (7.33 mmol) of potassium-t-butoxide in 20 ml DMF was stirred for 10 minutes. The mixture was heated to 110 °C and 0.630 ml of 2-fluoropyridine (7.33 mmol) was added. The reaction mixture was stirred at 110 °C for 2 hours at which point 177.8 mg (1.47 mmol) of KOtBu, dissolved in 0.2 ml DMF, and 0.126 ml (1.47 mmol) of 2-fluoropyridine were added. The mixture was stirred for an additional 2 hours at 110 °C. After 2 hours an additional 177.8 mg (1.47 mmol) of KOtBU, dissolved in 0.2 ml DMF, and 0.126 ml (1.47 mmol) of 2-fluoropyridine were added and the mixture was stirred again for 2 hours at 110 °C. The reaction was then allowed to cool and then poured into a 200 ml ice/water mixture. The aqueous solution was saturated with sodium chloride and extracted three times with 150 ml of chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The resulting oil was chromatographed by preparative HPLC using 1% methanol:chloroform. The product containing fractions were concentrated to provide 1.32 g (3.79 mmol, 51.7%) of product which was recrystallized from ethyl acetate in two crops to yield 692 mg of a white solid. The solid was dissolved in 10 ml chloroform:10 ml diethylether and ethereal hydrogen chloride was added. The precipitated salt was dried 2 hours at 80 °C and 2 hours at 111 °C to provide 679 mg (25.2%) of 6-O-demethyl-6-O-(pyridin-2-yl)galanthamine hydrochloride, m.p. 250-251 °C (dec).

ANALYSIS:			
Calculated for $C_{21}H_{22}N_2O_3 \cdot HCl$:	63.71%C	6.11%H	7.08%N
Found:	63.86%C	6.01%H	7.03%N

EXAMPLE 15

6-O-Demethyl-6-O-trifluoromethylsulfonylgalanthamine hydrochloride

A stirred solution of 2.0 g (7.33 mmol) of 6-O-demethylgalanthamine in 8 ml of dry pyridine was cooled in an ice/salt bath. To the solution was added slowly dropwise over several minutes 1.23 ml (2.07 g, 7.34 mmol) of triflouromethanesulfonic acid anhydride. The solution was allowed to warm to room temperature and stirred for 16 hours. The solution was poured into water/ice/chloroform, dried (Na_2SO_4), filtered and concentrated to an oil. The material was dissolved in chloroform and flash chromatographed on silica gel, eluting with 1% methanol/chloroform followed by 2% methanol/chloroform. The pure product-containing fractions were combined and concentrated to provide 0.625 g of a yellow solid. The material was dissolved in ether and the hydrochloride salt precipitated by addition of ethereal HCl, isolated by filtration, washed with ether and dried to provide 6-O-demethyl-6-O-trifluoromethylsulfonylgalanthamine hydrochloride, m.p. 219-220 °C.

ANALYSIS:			
Calculated for $C_{17}H_{18}F_3NO_5S \cdot HCl$:	46.21%C	4.33%H	3.17%N
Found:	45.79%C	4.29%H	2.86%N

EXAMPLE 16

6-Demethyl-6-O-(t-butyldimethylsilyl)galanthamine hydrochloride

To a cold solution of 6-O-demethylgalanthamine (3.0 g, 11 mmol) and imidazole (1.9 g, 28 mmol) in 30 ml of dimethylformamide, was added dropwise a tetrahydrofuran solution of t-butyldimethylsilyl chloride (1M solution in THF, 12 ml, 12 mmol).

After stirring at ambient temperature for twenty hours, the mixture was poured into water, stirred for 5 minutes, and then extracted with ethyl acetate (3X). The organic layer was washed with water, saturated sodium chloride solution, and dried over anhydrous $MgSO_4$.

After filtering, the solvent was evaporated to give a yellow oil, 4 g; which was eluted on a silica gel column with 3% methanol/dichlorofmethane via HPLC. The desired fractions were combined and evaporated to afford a white solid, 2.5 g (60%) , m.p. 88-90 °C. This material was dissolved in methanol, acidified to pH 1 with etheral HCL, and then diluted with ether. The resultant white precipitate was collected and dried to give 1.7 g (36%) of the product as a colorless solid, m.p. 199 °C (dec.).

ANALYSIS:			
Calculated for $C_{22}H_{33}NO_3Si \cdot HCl$:	62.31%C	8.08%H	3.30%N
Found:	62.00%C	8.20%H	3.21%N

EXAMPLE 17

6-O-Demethyl-6-O-(triethylsilyl)galanthamine

To a cold solution of 6-O-demethylgalanthamine (3.0 g, 11 mmol) and imidazole (1.9 g, 28 mmol) in 35 ml of dimethylformamide, was added dropwise a solution of chlorotriethylsilane (1M solution in THF, 12 ml, 12 mmol).

After stirring at ambient temperature for 20 hours, the mixture was poured into water, stirred for 5 minutes, and then extracted with ethyl acetate (2X). The organic layer was washed with water, saturated NaCl solution, and then dried over anhydrous $MgSO_4$. Filtering and concentration of the filtrated afforded a yellow oil, 4.0 g (90%) , which was eluted on a silica gel column with 5% methanol/dichlorofmethane via HPLC. The desired fractions were combined and then evaporated to give a white solid, 2.4 g (57%), m.p. 128-130 °C. This material was recrystallized from ether to give white crystals, 1.4 g (30%), m.p. 128-130 °C.

ANALYSIS:			
Calculated for $C_{22}H_{33}NO_3Si$:	68.17%C	8.58%H	3.61%N
Found:	67.81%C	8.71%H	3.60%N

EXAMPLE 18

6-O-Demethyl-6-O-(triisopropylsilyl)galanthamine hydrochloride

To a cold solution of 6-O-demethyl-galanthamine (3.0 g, 11 mmol) and imidazole (1.9 g, 28 mmol) in 30 ml of dimethylformamide, was added dropwise a solition of triisopropylsilyl chloride (2.6 ml, 12 mmol) in 5 ml of diemthylformamide.

After stirring at ambient temperature for 20 hours, the mxiture was poured into 200 ml of water, stirred for 5 minutes and then extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with water, saturated NaCl solution, and dried over anhydrous $MgSO_4$.

After filtering the filtrate was evaporated in vacuo to a yellow oil (~4 g), which was eluted on a silica gel column with 3% methanol/dichloromethane via HPLC. The desired fractions were combined and evaporated in vacuo to a yellow solid, 3.5 g , m.p. 53-56 °C.

A 1.0 g sample of this material was dissolved in methanol, acidified to pH 1 with ethereal-HCl and then diluted with ether. The resultant white precipitate was collected and dried to give 1.0 g (90%) of the products as colorless solid, m.p. 235 °C (dec).

ANALYSIS:			
Calculated for $C_{25}H_{39}NO_3Si \cdot HCl$:	64.41%C	8.65%H	3.01%N
Found:	64.15%C	8.42%H	2.84%N

EXAMPLE 19

6-O-Demethyl-6-O-(trimethylsilyl)galanthamine

To a cold solution of 6-O-demethyl-galanthamine (3.0 g, 11 mmol) and imidazole (1.9 g, 28 mmol) in 30 ml of dimethylformamide was added chlorotrimethylsilane (1.0 M solution in DCM, 12 ml, 12 mmol) dropwise.

After stirring at ambient temperature for 20 hours, the mixture was poured into 200 ml of water, stirred for 5 minutes, and then extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with water, saturated NaCl solution and then dried over anhydrous $MgSO_4$.

After filtering, the filtrate was evaporated in vacuo to a yellow oil, 3.0 g. This oil was eluted on a silica gel column with 5% methanol/dichloromethane via HPLC. The desired fractions were combined, then evaporated to a white solid, 1.4 g (37%), m.p. 173-174 °C.

ANALYSIS:			
Calculated for $C_{19}H_{27}NO_3Si$: Found:	66.04%C 65.63%C	7.88%H 7.89%H	4.05%N 3.98%N

EXAMPLE 20

6-Demethoxygalanthamine hydrochloride

To a stirred solutin of1.0 g(2.47 mmol) of recrystallized 6-O-demethyl-6-O-trifluoromethylsulfonylgalanthamine and 33 mg (0.126 mmol of triphenylphosphine in 40ml of dry DMF was added 55.5 mg (0.248 mmol) of palladium(II)acetate, followed by 1.05 ml of triethylame and 0.185 ml of 96% formic acid. The solution was stirred at 60-65 °C for 10 hours, then allowed to cool to room temperature, poured into ice/$NaHCO_3$,extracted with chloroform, concentrated to an oil and flash chromatographed on silica gel, eluting with 1%, 2% and 5%methanol/chloroform, respectively. The product-containing fractions were combined and concentrated to provide 0.53 g of solid. The material was dissolved in chloroform, diluted with ether, filtered and the hydrochlorided salt precipitated by addition of ethereal HCl. The material was crystallized from acetonitrile to provide 0.315 g of a solid, mp 242-244 °C.

ANALYSIS:			
Calculated for $C_{16}H_{19}NO_2 \cdot HCl$: Found:	65.41%C 65.31%C	6.86%H 6.78%H	4.77%N 4.67%N

EXAMPLE 21

3-(alpha-Methyl)galanthamine hydrochloride

Cerium (III)chloride (1.63 g, 6.63 mmol) was heated at 130-140 °C for 2 hours then cooled and 22 ml of dry THF was added and the suspension was stirred overnight at room temperature. The suspension was then cooled in an ice/salt water bate and 2.2 ml of 3.0 M methyl magnesium bromide in diethyl ether was added. The mixture was stirred at ice bath temperature for 1.5 hours followed by the addition of a suspension of 1.25 g (4.39 mmol) of narwedine in 12.5 ml of THF. The resulting suspension wasstirred for 0.5 hour and then poured into ice/NH_4Cl/chloroform. The mixture was basified with sodium bicarbonate, extracted with chloroform, dried (N_aSO_4), filtered and concentrated to an oil. The oil was chromatographed by flash chromatography on silica gel eluting with chloroform followed by 2%methanol/chloroform/saturated ammonium hydroxide. The product containing fractions were combined and concentrated to provide 0.91 g of an oil. The oil was dissolved in ethyl acetate and flash chromatographed on silica gel, eluting with 2%, 5% and 10%, respectively, isopropyl alcohol/ethyl acetate (saturated ammonium hydroxide). The product containing fractions were combined and concentrated to provide an oil which was dissolved in ether, cooled and ethereal HCl was added... The suspension was filtered and the residue was washed with ether and

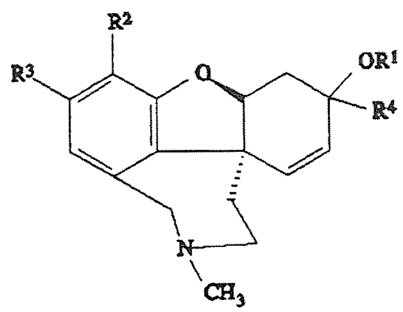
dried for 2 hours at 80 °C. The resulting solid was triturated with hot acetonitrile, centrifuge and dried to provide 0.20 g of product, m.p. 237-240 °C.

ANALYSIS:			
Calculated for $C_{18}H_{23}NO_3 \cdot HCl$:	63.99%C	7.16%H	4.15%N
Found:	63.83%C	7.15%H	4.00%N

It should be understood that this specification and examples are set forth by way of illustration and not limitation and that various modifications and changes may be made without departing from the spirit and scope of the present invention as defined by the appended claims.

Claims

1. A compound of the formula (II)



(II)

wherein

R^1 is hydrogen, $(C_1$-$C_{12})$alkylcarbonyl, $(C_1$-$C_{12})$alkoxycarbonyl, mono$(C_1$-$C_{12})$alkylaminocarbonyl or di$(C_1$-$C_8)$alkylaminocarbonyl;

R^2 is hydrogen, $(C_3$-$C_{12})$alkenylcarbonyloxy,$(C_3$-$C_{12})$cycloalkylcarbonyloxy, $(C_3$-$C_{12})$-cycloalkylaminocarbonyloxy, $(C_3$-$C_{12})$alkynyllcarbonyloxy, $(C_3$-$C_{12})$cycloalkyl$(C_1$-$C_{12})$-alkylcarbonyloxy, oxygen containing heterocyclyloxy, oxygen containing heterocyclylcarbonyloxy, sulfur containing heterocyclyloxy, sulfur containing heterocyclylcarbonyloxy, nitrogen containing heterocyclyloxy, nitrogen containing heterocyclylcarbonyloxy, haloalkylsulfonyloxy, $(C_1$-$C_6)$alkylsilyloxy;

R^3 is hydrogen, halo or $(C_1$-$C_4)$alkyl;

R^4 is hydrogen or $(C_1$-$C_6)$alkyl; with the proviso that R^1 and R^2 are not both hydrogen when R^3 and R^4 are hydrogen;

all geometric, and optical and stereoisomers thereof, or a pharmaceutically acceptable addition salt thereof.

2. A compound of the formula (II) as defined in claim 1,

wherein

R^1 is hydrogen, $(C_1$-$C_{12})$alkylcarbonyl, $(C_1$-$C_{12})$alkoxycarbonyl;

R^2 is hydrogen, $(C_3$-$C_{12})$alkenylcarbonyloxy, $(C_3$-$C_{12})$alkynylcarbonyloxy, $(C_3$-$C_{12})$-cycloalkylcarbonyloxy, $(C_3$-$C_{12})$cycloalkylaminocarbonyloxy, $(C_3$-$C_{12})$cycloalkyl$(C_1$-$C_{12})$-alkylcarbonyloxy, $(C_3$-$C_{12})$cycloalkylcarbonyloxy, halo$(C_1$-$C_6)$alkylsulfonyoxyl, $(C_1$-$C_6)$-alkylsilyloxy, pyridyloxy, thiomorpholinocarbonyloxy, furanylcarbonyloxy, thienylcarbonyloxy, tetrahydrofuranylcarbonyloxy, furanyloxy, thienyloxy, pyrrolidinylcarbonyloxy, tetrahydrofuranyloxy, piperidinylcarbonyloxy, azepincarbonyloxy, morpholinocarbonyloxy or tetrahydroisoquinolinylcarbonyloxy;

R^3 is hydrogen or halo;

R^4 is hydrogen or $(C_1$-$C_6)$alkyl;

with the proviso that R^1 and R^2 are not both hydrogen when R^3 and R^4 are hydrogen;

and all geometric, optical and sterioisomers and pharmaceutically acceptable addition salts thereof.

3. A compound of the formula (II) as defined in claim 1, wherein

R^1 is hydrogen, $(C_1\text{-}C_{12})$alkylcarbonyl or $(C_1\text{-}C_{12})$alkoxycarbonyl;

R^2 is $(C_3\text{-}C_{12})$alkenylcarbonyloxy,$(C_3\text{-}C_{12})$alkynylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkylcarbonyloxy, $(C_3\text{-}C_{12})$cycloalkyl$(C_1\text{-}C_{12})$alkylcarbonyloxy, pyridyloxy, furanoyloxy, morpholinocarbonyloxy or tetrahydroisoquinolylcarbonyloxy;

R^3 is hydrogen or bromine; and

R^4 is hydrogen or methyl.

4. A compound of the formula (II) as defined in claim 3, wherein

R^1 is hydrogen.

5. A compound of the formula (II) as defined in claim 4, wherein

R^3 and R^4 are hydrogen.

6. A compound of the formula (II) as defined in claim 4, wherein

R^2 is cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclohexylcarbonyloxy, methylcyclohexylcarbonyloxy, adamantylcarbonyloxy, adamantylmethylcarbonyloxy, 2-methylpropenylcarbonyloxy, 2-propynylcarbonyloxy, cycloheptylaminocarbonyloxy, cyclohexylaminocarbonyloxy, morpholinocarbonyloxy or tetrahydroisoquinolinylcarbonyloxy.

7. The compound of the formula (II) as defined in claim 1, which is (6-O-demethyl)-6-O-(1,2,3,4-tetrahydroisochinolin-2-yl)-carbonyl)-galanthamine or a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition, which comprises a compound of the formula (II) as defined in claim 1 and a pharmaceutically acceptable acid addition salt thereof.

9. Use of a compound of the formula (II) as defined in claim 1 for the preparation of a medicament being useful for the treatment of memory dysfunction characterized by decreased cholinergic function.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 11 5959

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP-A-0 236 684 (DAVIS BONNIE) * column 2, line 24 - line 27 * ---	1,8,9	C07D491/06 A61K31/55 //(C07D491/06, 307:00,223:00)
A	CHEMICAL ABSTRACTS, vol. 112, no. 13, 26 March 1990, Columbus, Ohio, US; abstract no. 112096y, * abstract * & NL-A-8 800 350 (STICHTING BIOMEDICAL RESEARCH AND ADVICE GROUP) ---	1,8,9	
A	WO-A-88 08708 (DAVIS BONNIE) * pages 5,6,16 * ---	1,8,9	
A	WO-A-92 20327 (SNORRASON ERNIR) * page 43; claim 20 * ---	1,8,9	
A	EP-A-0 535 645 (HOECHST-ROUSSEL PHARM. INC.) * compounds IIIa,Va,VIIa * ---	1,8,9	
A	THE MERCK INDEX 10TH EDITION , MERCK & CO., INC. , 1983 RAHWAY, N.J., U.S.A. * No. 4210 * -----	1,8,9	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	2 February 1995	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
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